FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

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The problem, policy, history, & fix

CLEANING UP CELL-LINE CROSS-CONTAMINATION

by Christopher Wanjek

If only mouse cells had ears, whiskers, and a tail. These would make it much easier to identify the type of cross-contamination that for decades has plagued laboratories, invalidated years of research, sidetracked careers, and possibly squandered millions of research dollars.

In well-documented cases that highlight both the range and ubiquity of the situation, guinea pig cells have turned out to be mouse cells, ovarian cancer cells have been disguised as breast cancer cells, and, in extreme cases, some cell lines have been unidentifiable.

NIH is not immune, neither in the research performed here nor in the products produced. Many cell lines from reputable sources are accidentally mischaracterized or masquerading as another kind of cell unbeknownst to the supplier or user.

At least three lines in the respected and much utilized NCI-60 cancer cell lines are mischaracterized—such as MCF-7/AdrR, which was once thought to be a daughter of the breast cancer line MCF-7 but in reality is an ovarian cancer cell line.

More than 15 percent of cell lines

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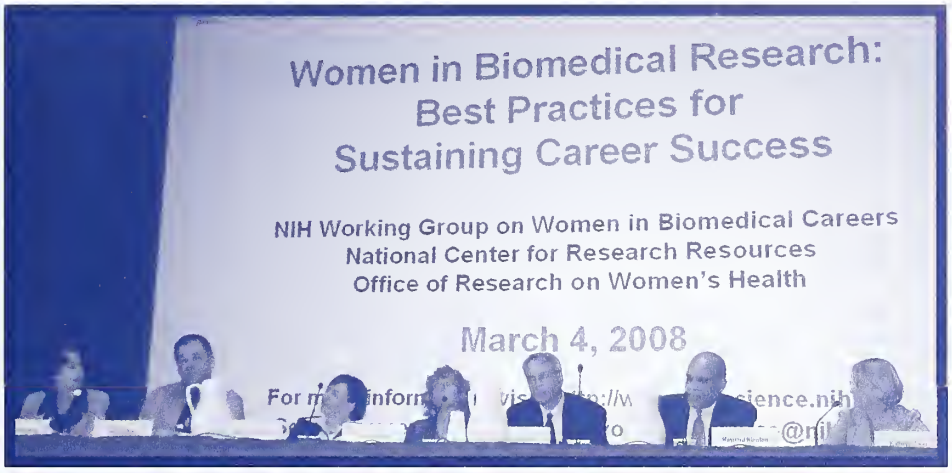
BIAS AGAINST WOMEN IN SCIENCE: IT'S STILL THERE, AND IT'S GOT TO GO

by Fran Pollner



Fran Pollner

Agents of Change: *Discussing NIH initiatives to correct gender imbalances are (left to right) Joan Goldberg, executive director, American Society for Cell Biology; Jeremy Berg, NIGMS director; Joan Schwartz, assistant director, OIR; Valerie Florance, deputy director for extramural programs, NLM; Walter Schaffer, senior scientific advisor for extramural research; Raynard Kington, NIH deputy director; and panel chair Kathryn Zoon, director of intramural research, NIAID*

If there is such a thing today as a post-feminist world, it's not to be found just yet in much of the biomedical research arena, where various obstacles thwart the advancement of women scientists to commanding positions, such as department head at a research university or lab chief at NIH.

But rigorous documentation of attrition rates for women beyond the postdoctoral level has set the stage for designing and implementing systematic remedies, and large numbers of people in the field are determined to turn things around.

"This is not something we ought to be doing because it's nice to do. It's something we have to do" because the future of biomedical research depends on it, said NCRR Director Barbara Alving, opening a daylong conference here on "Best Practices for Sustaining Career Success" for women in biomedical research.

The military biomedical research sector, as well as successful businesses, "recognized this long ago" and have developed "innovative practices" to attract and retain women at the highest levels, Alving said, presaging several talks on the day's agenda.

Framing the Issues: Numbers Talk

Women have become 50 percent of medical school applicants and graduates and they are 46 percent of assistant deans and 33 percent of associate deans—but only 12 percent of deans of U.S. medical schools, said keynoter

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A Life Remembered: Joseph Edward Rall, 1920–2008

Michael Gottesman

Joseph "Ed" Rall, one of the lions of NIH who helped to define its modern intramural research program and, in the 1950s, to establish a stable academic community within a rapidly expanding government agency, died on February 28. He was 88 years old.

Often in my own role as DDIR, I marvel at the lasting effect Ed had on the style and substance of the IRP. I'd like to share my thoughts on his life, as well as the sentiments of those who worked closely with him.

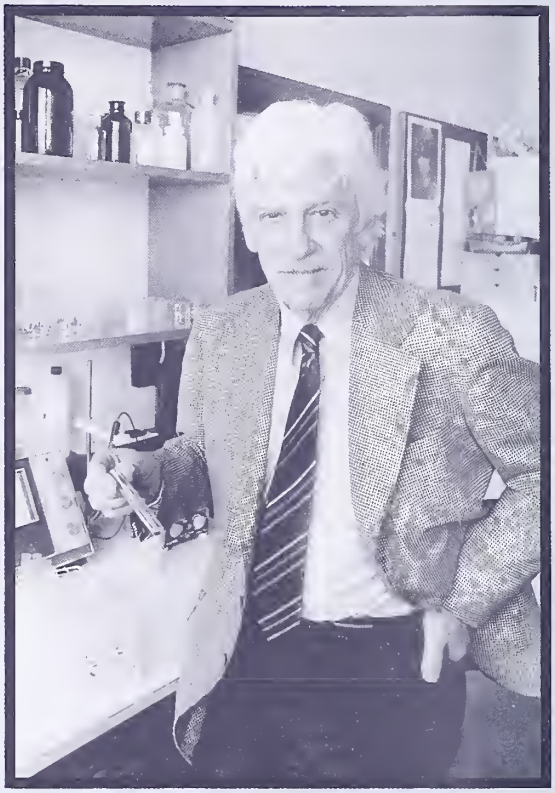
Rall was a consummate scientist; a charismatic mentor, recruiter, and scientific director; and an engaging Renaissance man. He arrived at NIH in 1955 and built from scratch the Clinical Endocrinology Branch in the newly formed National Institute of Arthritis and Metabolic Diseases. He hired a diverse crew of scientists with seemingly disparate backgrounds to focus on a single endocrine organ, the thyroid, a vision that soon produced one of the most productive branches at NIH and helped earn NIAMD international recognition.

In 1962, Rall became scientific director of NIAMD (where I was a research associate from 1971 to 1974) and continued in that position for more than 20 years through the institute's various transformations into the National Institute of Diabetes and Digestive and Kidney Diseases. From 1981 to 1982, he was also acting NIH deputy director for science before stepping into that position full time with its current title, deputy director for intramural research, from 1983 to 1991. He never left NIH, transitioning to emeritus status in 1995.

For more than 40 years, Rall was a major force at the NIH, first with his groundbreaking research on the thyroid and then with his leadership skills guided by a broad knowledge of multiple scientific disciplines. He lived and breathed science and eloquently championed and defended the scientific process. His colleagues at NIH and around the world comprise a veritable Who's Who in biomedical and clinical research.

"Ed was remarkable in his drive, his passion to help other scientists—young scientists in particular—to foster a sound scientific attitude," said Baruch Blumberg, a long-time friend who won a 1976 Nobel Prize for his work on hepatitis B.

Blumberg, whose research on polymorphisms at NIAMD aided his NIH-funded research on hepatitis B later at the Fox Chase Cancer Center in Philadelphia, recalled his frequent conversations with Rall about the scientific process and how much these had influenced his career. "He gave a lot of himself to other people," he said.



J. Edward Rall at a lab in New Zealand

Under Rall's guidance, the Clinical Endocrinology Branch soon became a Mecca for bright endocrinologists from around the world, including Rosalind Pitt-Rivers, co-discoverer of triiodothyronine; Nino Salvatore, a Fogarty scholar who later helped reform the Italian educational system; and Jamshed Tata, a developmental biologist from Britain's National Institute for Medical Research.

"The best people from around the world came [to the Clinical Endocrinology Branch] to work," said Ira Pastan, one of those endocrinologists as well as a close friend, who began working with Rall in the 1960s and who is now chief of NCI's Laboratory of Molecular Biology. "Ed's intelligence and personality attracted them. He was fun to talk science to."

"Ed had excellent scientific judgment; he was always interested in the science, always encouraging," said Marshall Nirenberg, another friend who, while at NIAMD, performed his famed RNA and poly-U experiments, a preamble to the research on the genetic code that matured after his transition to the National Heart Institute in 1962 and which led to his 1968 Nobel Prize.

Rall was in fact involved indirectly in several Nobel Prize–winning research efforts, from his

encouragement of Nirenberg—then a junior postdoc at NIAMD before his rapid rise to prominence in 1962—to the remarkable stretch of highly productive research that occurred at NIAMD during his tenure as scientific director: namely, that of sailing buddy Christian Anfinsen, who won a 1972 Nobel Prize for protein chemistry; Martin Rodbell, who won a 1994 Nobel Prize for GTP-binding and G proteins; and Blumberg.

A member of the National Academy and the first person at NIH named to the executive rank in the Senior Executive Service, Rall himself was a man of acute scientific acumen who authored more than 160 journal articles.

His first major contribution to science came in the early 1950s, as a graduate student at the Mayo Clinic in Rochester, Minn., and then postdoc at Memorial Sloan-Kettering in New York, where he was among the first to use radioactive iodine to study thyroid function. It was here that he met Jacob "Jack" Robbins, a meeting that would blossom into a nearly 60-year friendship. Robbins helped build the Clinical Endocrinology Branch with Rall, succeeded him as chief in 1962 for the next quarter of a century, and remains an active volunteer in the branch today.

With Robbins and others, Rall introduced hormone treatment to thwart the development of thyroid nodules and cancer from radiation fallout from atomic bomb testing on the Bikini Atoll. In the landmark 1960 paper by Robbins and Rall in *Physiological Reviews*, entitled "Proteins Associated with the Thyroid Hormones," the two colleagues surveyed everything known about thyroid hormones in circulation and the effect of the binding proteins on their bioactivity. They developed the then-revolutionary, now classic, hypothesis that the free hormone, only a tiny fraction of the total, was the active molecule.

Robbins joked of how he stuck it out in bench work while Rall moved into the leadership role of scientific director and deputy director, which naturally suited him. "He was a polymath; every field was easy for him," Robbins said.

Nirenberg added that Ed followed in the footsteps of his father, who was president of North Central College, a small liberal arts school outside of Chicago. Rall in essence became the dean of NIH.

"'Ed surfed through life, riding the crests of the waves, recognizing where they began and where they were headed," said Robbins at Rall's memorial service on March 4. This keen insight that embraced mathematics, physics, chemistry, biology, and clinical studies enabled Rall to grease the wheels and "make things happen" at NIH, Robbins later recalled. "He had high standards. If you were smart, you had his attention."

"He was that element at NIH with profound respect for basic research," said Blumberg.

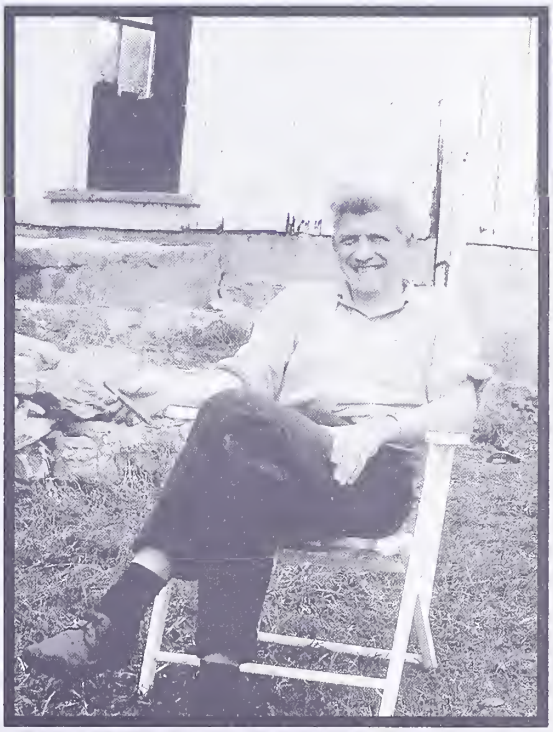
Socially, Rall was a "warm and inviting man" who hosted countless parties at his house, said Pastan, who remembers banging his head hard during one backyard soccer game there. Rall's favorite sport was tennis. He, Pastan, David Davies, Cal Baldwin, Mort Lipsett, Bill Eaton, and others from NIH would meet early in the morning before work at the Linden Hill tennis club.

"Ed was enthusiastic about everything he did, including tennis," Pastan laughed. "We often joked that all the important decisions about the NIH were done at Linden Hill."

Other pastimes included sailing, skiing, skating the C&O canal, music, and a love of literature and words. "He was a superb public speaker," Nirenberg said.

Rall shared a large working farm on the banks of the Potomac with Robbins, Blumberg, and Wilfred Rall of NIDDK, a distant cousin. This was the opposite of a timeshare, Robbins said, because the four families would go there not when it was empty but rather when everyone could make it. The families, now in their second and third generations, still try to meet.

"Ed was interested in everything," Robbins said. Then, pausing to think of all he had just relayed about Rall's life, he added: "We'll really miss him." ■



Baruch S. Blumberg

Ed Rall at Antietam Meadows farm in Sharpsburg, Maryland, fall 1968

Bias Against Women in Science

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Fran Pollner

***Camaraderie**: (left to right) Kathryn Zoon, NIAID scientific director; Barbara Alving, NCRR director and conference chair; and Naomi Luban, chief of laboratory medicine, Department of Pediatrics, Children's National Medical Center, Washington*

Nancy Andrews, dean of the Duke University School of Medicine, Durham, N.C., who upon her appointment published a piece in the November 2007 issue of the *New England Journal of Medicine*, "Climbing Through Medicine's Glass Ceiling."

Deans, Andrews observed, emerge not from the pool of associate deans but from department chairs, a far more elusive inner circle for women, who hold 8.5 percent of these positions. Although junior women tend to downplay gender bias as a major problem for women in academic medicine, citing work-family balance as the greatest challenge, marginalization rooted in gender bias is felt increasingly by senior women as they move up in the ranks, she said.

Andrews advocated relentless "nagging" to change the facts on the ground—like upping the numbers of women on speakers' lists and search committees and removing administrators with poor track records in hiring and retaining women.

More numbers—documenting just how few women do move up in the ranks—were offered by Timothy Ley, associate director of basic science and professor of medicine at the Washington University Medical School in St. Louis, and Phoebe Leboy, president of the Association for Women in Science and professor of biochemistry at the University of Pennsylvania School of Dental Medicine in Philadelphia.

At each step on the NIH grant-funding ladder, fewer women apply—and not because they are less successful at being selected, Ley reported. There is little difference among the three groups of degree-holders—Ph.D, M.D., and M.D.-Ph.D.—with the most dramatic falloff occuring at the late postdoctoral stage between the K23 and KO8 levels, when about half of the women applicants are lost; when the first RO1 application level is reached, the ratio of male to female applicants is 2–3:1, he said. "Among those who do apply, the success rates are identical . . . but women are leaving the academic medical career path at double and triple the rate of men." Ley observed that that path "was created by men for men."

"The objective evidence," Leboy concurred, "is that women score very well on grant applications." In 2006, there were more women than men in the top 10 percent fundable NIH grant applications, she said, but the other side of that story is that there are fewer grants per PI among women, fewer dollars per grant awarded women, a lower reapplication success rate for women, and a nearly complete absence of women on the "really big and increasingly popular center grants." The last item, she noted, reflects the nearly exclusive selection of men as PIs by the participating institutions.

Fran Pollner

***Data miners:** Timothy Ley and Phoebe Leboy*

Tracking the progress of women with Ph.D.s in biochemistry, molecular biology, cell biology, developmental biology, and neuroscience at academic health centers and research universities, Leboy reported the results of a survey of 58 institutions that in November 2007 had advertised faculty positions in these fields. Far fewer women applied than would be expected based on the percentage of women in the potential Ph.D. applicant pool.

For instance, although women hold 43 percent of Ph.D.s in biochemistry, they were only 17 percent of applicants for junior faculty positions in biochemistry departments; the statistics for cell and developmental biology were closer to 30 percent but well under the expected 48 and 52 percent. "Women are avoiding tenure-track faculty jobs," Leboy said, noting that this study did not address how many women were actually hired.

She noted that the "proportion of tenure-track and tenured women has reached a plateau of less than 60 percent of expectations and is now declining." These data, she said, support the finding that women are more likely to opt out at the point of transitioning beyond the postdoc stage, reported in the November 2007 issue of *EMBO Reports*.*

The question of why, however, remains, she added, noting that although the EMBO report suggests that women have less confidence, the "chilly climate" for women in academia may go further in explaining why "smart young women" are disinclined to pursue biomedical careers there. There are no data, she added, on how many of these women enter the private workforce.

In all arenas, it was mentioned throughout the conference, there are next to no data on minority women in science.

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*"Falling Off the Academic Bandwagon," by members of the NIH Postdoctoral Fellows Subcommittee of the Second Task Force on the Status of NIH Intramural Women Scientists

How Does Industry Do It?

Anticipating a serious shortage of skilled employees, private sector companies in the late 1980s and early 1990s decided that hiring more women—and, especially, retaining them—would be a solution and key to future success, according to Asif Dhar, biomedical informatics practice leader at Deloitte Consulting in McLean, Va., and Jo Ellen Helmer, a partner at Ernst & Young LLP in Chicago.

Deloitte started the Women's Initiative in 1993, focusing on two main aspects: providing a network and mentorship for women throughout their careers and allowing for a nonlinear progression of careers. Employees can customize and adjust the pace, workload, location schedule, and role they would like to play in the company according to the stage of life they are in.

Flexibility is also the key in keeping women in the workforce at Ernst & Young. Flexible work hours, mentoring, and networking are essential, and such items as longer maternity leave have greatly added to the satisfaction of women, Helmer said. In fact, the models originally developed for women have been adopted for the workforce in general and have proved to increase overall productivity.

Both speakers emphasized the importance of measuring the success of the program and making senior staff accountable. At Ernst & Young, it is impossible to reach maximum points (and therefore maximum pay bonuses) if the "inclusiveness" goals have not been achieved.

—Christiane Jost

Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH

Susan Gottesman: Small RNAs and Adapting to Stress

by Gail Seabold

Holly Dimitropoulos

Susan Gottesman

Susan Gottesman, co-chief of NCI's Laboratory of Molecular Biology and chief of its Biochemical Genetics Section, presented the fourth lecture in the "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" on March 4.

Gottesman's seminar, entitled "Stress Adaptation via Regulatory RNAs," focused on her recent work examining the role of small noncoding RNAs in regulating translation and messenger RNA stability. Her laboratory is interested in novel mechanisms for gene regulation and how these mechanisms contribute to global control circuits in *Escherichia coli.*

Conducting a genome-wide collaborative study, Gottesman identified 17 novel small RNAs and six new short mRNAs. Study of the function of these new small RNAs is ongoing, but many of them appear to be involved in translational regulation.

Another genome-wide search identified small RNAs that bind to the RNA chaperone Hfq, a protein that facilitates the interaction of small RNAs with messenger RNA. By base-pairing with messenger RNA, small RNAs can influence the translation of messenger RNA in a positive or negative manner, depending on the environment of the cell. Gottesman's work suggests that small RNAs are important components of regulatory circuits and play a role in regulating stress responses to conditions such as low iron or the accumulation of toxic glucose phosphate.

For example, small RNAs can limit the production of nonessential iron-binding proteins, making iron more available to essential proteins, and cause the degradation of mRNA for the glucose transporter of the phosphotransferase system, thereby reducing the uptake of glucose and production of glucose phosphate.

Gottesman's collaborations with other NIH investigators include the identification with Gisela Storz, NICHD, of some small noncoding RNAs in bacteria and with Michael Maurizi and Sue Wickner, both of NCI, on previous work that focused on the role of energy-dependent proteases in regulation of the degradation of abnormal and misfolded proteins, as well as their involvement in setting critical levels for regulatory proteins. This work led to Gottesman's election to the American Academy of Microbiology, the National Academy of Sciences, and the American Academy of Arts and Sciences.

Gottesman has also served as an editor of the *Journal of Bacteriology, Genetics,* and *Annual Review of Microbiology* and as an editorial board member of *Genes & Development* and *Molecular Microbiology.* She has had leadership positions in the ASM, ASBMB, Genetics Society, and AAAS and is currently on the NAS council. Among her many awards are an NIH Director's Award and NIH Merit Award. ■

Starring Roles

Susan Gottesman grew up on Long Island and became interested in microbiology after reading *Microbe Hunters* by Paul de Kruif, a "historical fiction" about such early microbiologists as Antonie van Leeuwenhoek and Louis Pasteur. Gottesman received her B.A. in biochemical sciences from Radcliffe College (Cambridge, Mass.), magna cum laude, and her Ph.D. in microbiology and molecular genetics from the Graduate School of Arts and Sciences, Harvard University, Cambridge. She came to NIH in 1971 to pursue postdoctoral training with Max Gottesman (formerly at NCI, now at Columbia University), then went back to Boston as a research associate in the MIT laboratory of David Botstein, and returned to NIH in 1976 as a senior investigator in the Laboratory of Molecular Biology, NCI, where she continues today. She is married to Michael Gottesman, deputy director for intramural research, and they have two children and two granddaughters. ■

The Roberts Legacy

The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors the memory of its namesake. who was chief of the Laboratory of Cell Regulation and Carcinogenesis at NCI from 1995 until her death May 26, 2006. A research leader at NIH for 30 years, Roberts was a pioneer in the field of carcinogenesis, autoimmune disease, and wound healing, with special contributions to current knowledge of transforming growth factor–β. She was among the top 50 most-cited authors for her published work from 1982 to 2002 (see "The Shining Legacy of Anita Roberts, *The NIH Catalyst,* Sept.–Oct. 2007). ■

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Climate Change

Early last year, in response to a National Academies report on bias and barriers facing women in academic science and engineering, NIH Director Elias Zerhouni established the NIH Working Group on Women in Biomedical Careers. This conference was the objective of one of the group's 11 subcommittees.

NIH Deputy Director Raynard Kington, chair of the subcommittee on research on the efficacy of programs to reduce gender bias, observed that with the will to change, things can happen quickly, as was the case with the Director's Pioneer Awards, part of the NIH Roadmap: None of the first-year awardees were women, but 46 percent of the second-year cohort were. The change was effected not by targeting women for awards but by making the process fairer, he said.

His subcommittee is canvassing programs across the country aimed at "transforming the culture" and has found that most of them are small, under five years old, and unevaluated for impact. NIGMS, he said, has issued an RFA to study interventions to promote biomedical research careers and their effectiveness.

Addressing the climate at home, Joan Schwartz, assistant director, OIR, and a member of several subcommittees aimed at recruiting, retaining, and advancing women at NIH, outlined some of the programs under consideration or underway:

- expanding access to childcare both on and off campus
- providing a tenure-track investigator or PI with a temporary lab manager during times of needed extended leave
- recruitment of dual-career couples, facilitated through a regional consortium, of which NIH is a founding member
- encouraging teleworking
- creation of a trans-NIH mentoring committee; training PIs in mentoring skills and senior investigators, postdocs, and graduate students in leadership skills
- conducting focus groups among NIH women to learn how to promote taking the first step beyond the postdoc level

Asked for some statistics on women lab chiefs at NIH, Schwartz noted that the percent has increased over the last 10 years—from 4 to 16 percent.

She issued an oft-repeated invitation that attendees "please send in any thoughts you have." To do so, write to:

<womeninscience@nih.gov>.

Annual Review

Selected NIH Intramural Research Accomplishments 2007

Discoveries that add to the body of knowledge about normal and abnormal biological functions and behavior

Identification of disease genes

- Detection in a genome-wide association study of new genetic variants in a previously unsuspected region on chromosome 8q24 associated with increased risk of prostate cancer in men of European ancestry (NCI-DCEG, NCI-CCR)
- Identification in a genome-wide association study of breast cancer of four single-nucleotide polymorphisms in the *FGFR2* gene that are highly associated with sporadic postmenopausal breast cancer in women of European ancestry (NCI-DCEG, NCI-CCR, NCI-DCP)
- Discovery of *HAX1* mutations in some cases of autosomal recessive severe congenital neutropenia (NCBI/NLM)
- Identification of a homozygous point mutation in the 3^1 untranslated region of the p14 gene (also known as the *MAPBPIP* gene) as the cause of a newly characterized syndrome combining severe congenital neutropenia, hypopigmentation, B-cell defects, and short stature (NCBI/NLM)
- Identification of mutations in the *STAT3* (signal transducer and activator of transcription 3) gene as the cause of hyper-IgE syndrome, also known as Job's syndrome (NIAID, NHGRI, NCI, NCBI, CDER)
- Discovery using retrovirus-mediated RNA interference of several unexpected roles of the *DISC1* (disrupted-in-schizophrenia–1) gene in the development of new neurons in the adult hippocampus (NICHD)
- Identification of the genes that cause—and elucidation of the pathways leading to—recessive osteogenesis imperfecta (OI), a relatively rare form of OI at the most severe end of the clinical spectrum (NICHD)
- Identification in a genome-wide association scan of genetic variants in the *FTO* gene associated with obesity-related traits in BMI, hip circumference, and body weight, providing a novel entrée to corresponding pathways and a target for possible therapeutic approaches (NIA)
- Identification of a deletion mutation of *ITPR1* as the cause of spinocerebral ataxia 15, an inherited adult-onset neurological disease, further implicating calcium regulation in the pathobiology of this disorder and enabling an accurate molecular diagnosis that can be applied presymptomatically (NIA, NINDS, NICHD)
- Identification of a new gene, *FANCN*, that is defective in Fanconia anemia patients of complementation group N and also resembles *PALB2*, suggesting it is also a breast cancer susceptibility gene (NIA)
- Identification of a single ancient allele of the insulin-like growth factor gene as the major contributor to small size across dog breeds, shedding light on the evolution of complex traits (NHGRI)
- Identification of at least four new genetic variants associated with increased risk of diabetes (*IGF2BP2, CDKAL1, CDKN2A*, and *CDKN2B),* bringing to at least 10 the number of genetic variants confidently associated with increased susceptibility to type 2 diabetes (NHGRI)
- Identification of a common variant of the *STAT4* gene, which encodes a protein involved in immune cell activation and differentiation, as a contributor to susceptibility to two autoimmune diseases, rheumatoid arthritis and systemic lupus erythematosus (NIAMS)
- Identification in a genome-wide association study of a locus on chromosome 9 that includes two rheumatoid arthritis susceptibility genes, *TRAF1* (TNF receptor–associated factor 1) and *C5* (complement component 5) (NIAMS)
- The finding on FMRI scans that two gene variants implicated in schizophrenia interact to degrade the brain's ability to process information and consequently impair working memory in otherwise normal adults (NIMH)

Important new animal models

- Demonstration in a mouse model that anthrax lethal toxin produces shock that is insensitive to fluid administration and that the anthrax edema toxin produces much greater decreases in blood pressure than lethal toxin, suggesting that both the pathogenesis and the response to conventional therapy for anthrax-induced shock differ substantially from conventional septic shock and require new management approaches (CC, NIAID)
- Development of an experimental uveitis model by exposing mice to the same retinal antigen but under different inductive conditions, eliciting a disease that differs from the currently used model clinically, histologically, and immunologically and shedding light on the heterogeneous nature of uveitis in humans (NEI)
- Demonstration in mice of a potential new route to prevention of salivary gland damage—by protecting the microvascular endothelial cells in the gland—in patients undergoing irradiation for head and neck cancer (NIDCR, NCI)
- Demonstration for the first time that siRNA as expressed by a lentiviral vector is both safe and efficacious in a large-animal model in a study that achieved downregulation of CCR5 expression in nonhuman primates, with evidence of continuing SIV resistance to simian immunodeficiency virus in transduced cells for at least two years (NHLBI)
- Identification in animal models of infection that the production of high concentrations of the novel phenol-soluble modulins is key to the severity of community-associated methicillin-resistant staph infections (NIAID)
- Study in mouse models of neurodegeneration of the newly identified protective pathway—called preemptive quality control—that attenuates the adverse consequences of protein misfolding in the endoplasmic reticulum (NICHD)
- Demonstration of a potential role of glutamate-dopamine interactions in a mouse model of schizophrenia lacking functional GluR1 (AMPA) glutamate receptors (NIAAA)
- Description of a novel, brain-penetrant, orally active corticotropin-releasing factor receptor antagonist with efficacy in animal models of alcoholism (NIAAA)
- Demonstration in a rat model of human metabolic syndrome that the green tea polyphenol epigallocatechin gallate lowers blood pressure, improves endothelial dysfunction, increases insulin sensitivity, and protects against myocardial ischemia and reperfusion injury as well as conventional therapy with the ACE inhibitor enalapril (NCCAM)
- Findings in mouse studies that neurons express several Toll-like receptors (TLRs), whose levels increase and promote cell death in response to stroke-induced energy, establishing an adverse effect of TLR activation in neurons and inflammatory immune cells that may worsen the outcome of a stroke and providing a rationale for therapeutic stroke interventions that target TLR-signaling pathways (NIA)
- The finding that resveratrol, a polyphenolic compound found in red grapes, improves health and survival in

middle-aged overweight male mice on a high-calorie diet, the first demonstration of health and survival effects of resveratrol in mammals (NIA)

- The finding in a rat-reinstatement model that injections of peptide YY3-36, a gastrointestinal-derived hormone, decreased typical cue-induced high-fat food seeking behavior, suggesting a role for this peptide in preventing relapse of poor eating habits among people on a diet (NIDA)

Basic discoveries in cell, molecular, and structural biology with implications for the treatment of human disease

- Determination of the molecular composition of tip links, which connect the tops of stereocilia found on sensory cells in the inner ear and are thought to convey the force to gates in mechanoelectrical transduction channels (NIDCD)
- Twin study evidence that dichotic listening—the ability to identify and distinguish different stimuli presented simultaneously to each ear, which is related to normal interhemisperic information processing—is a highly heritable trait (NIDCD)
- Enhanced understanding of ABC transporters with the finding that "silent" mutations in a multidrug-resistance gene affect cancer diagnosis and treatment (NCI-CCR)
- Keener insight into DNA damage with the visualization of DNA breaks in living cells and the finding that ATM (ataxia-telangiectasia mutated kinase) prevents the persistence and propagation of DNA breaks (NCI-CCR)
- Elucidation of the role of chaperones in the identification of an acetylation site in the middle domain of Hsp90 that regulates its function, coupled with the finding that asymmetric deceleration of ClpB or Hsp104 ATPase activity unleashes protein-remodeling activity (NCI-CCR)
- Finding that junctional adhesion molecule–C regulates the vascular endothelial barrier, advancing the understanding of angiogenesis (NCI-CCR)
- Discovery of nonhistone Scm3 as a crucial component of the core of yeast centromere, advancing knowledge of chromosome biology (NCI-CCR)
- Finding that frequent engagement of the classical and alternative NF-κB pathways by diverse genetic abnormalities promotes cell survival in multiple myeloma (NCI-CCR)
- Discovery in a well-characterized clinical model of acute inflammation that inhibition of cyclooxygenase-2 (COX-2) by drugs such as ibuprofen modulates gene expression besides the COX-2 cascade; these changes in gene expression may be associated with both the analgesic and the toxic effects of these widely used drugs (NINR, NIDCR)
- Finding that acetaminophen, widely used for pain management as an alternative to drugs like ibuprofen and COX-2 inhibitors, alters the release of inflammatory mediators and expression patterns of genes related to COX-2 much as drugs like ibuprofen and COX-2 inhibitors do, raising the possibility of similar adverse effects as well (NIDCR, NINR)
- Elucidation of novel mechanisms by which omega-3 long-chain polyunsaturated fatty acids and macular xanthophylls influence angiogenic, inflammatory, and cell-survival pathways implicated in the pathogenesis of age-related macular degeneration, diabetic retinopathy, and retinopathy of prematurity (NEI, NIAAA, ODS)
- Discovery that expansion of Th17 cells in normal human blood by IL-2 is a cause of human inflammatory and autoimmune diseases and that antagonism of Th17 by IFN-γ and IL-27 could be used for treatment of two human chronic ocular inflammatory diseases, uveitis or scleritis (NEI)
- Identification of progenitor cells residing in a unique extracellular niche in human and mouse tendon that have universal stem-cell characteristics, including clonogenicity, multipotency, and self-renewal capacity, thereby opening up new approaches to help mend torn or degenerating tendons (NIDCR)
- Establishment of the existence of a dysregulated signaling network in head and neck cancer, thereby identifying novel molecular targets for the prevention and treatment of these malignancies (NIDCR, NCI)
- Discovery of random cell migration and self-organization during gland development that lead to tissue engineering of three-dimensional salivary gland precursors by self-assembly of dissociated cells (NIDCR)
- Identification of a much more extensive mitochondrial phosphoproteome signaling pathway than previously recognized, including the identification of specific phosphorylation sites within the entire oxidative phosphorylation processes and the demonstration that phosphorylation is a regulatory mechanism of MnSOD activity (NHLBI)
- Elucidation of the catalytic process by which hemoglobin converts nitrite to nitric oxide, with implications for the understanding of normal physiology and the therapeutic application of this "new chemistry" (NHLBI)
- Discovery of a novel immunogenic antigen encoded by human endogenous retrovirus type E that is selectively expressed in the majority of clear-cell kidney cancers but not in normal tissues and elicits immune responses resulting in regression of metastatic kidney cancer after allogeneic hematopoietic cell transplantation (NHLBI)
- Discovery of a regulatory role for CD40 ligand in loss of bone mass, revealed in a study involving patients with X-linked hyper-IgM syndrome (NIAID, CC, NCI)
- New insight into potential cellular and molecular mechanisms underlying the genetic link between CX3CL1 and CX3CR1 and atherosclerosis, suggesting that this chemokine–chemokine receptor pair may be considered a pro-inflammatory target in the prevention and treatment of atherosclerosis (NIAID)
- Discovery of the first component, called TRC40, of a novel membrane protein insertion pathway for tail-anchored proteins, adding to the knowledge of normal cellular function (NICHD)
- Findings related to the role of brain-derived neurotrophic factor in depression and anxiety that suggest that BDNF is a target of antidepressants (NICHD, NIMH)
- Findings that several amino acid derivatives of β-cyclodextrin block ion conductance through pores formed by both anthrax lethal toxin and *Staphylococcus aureus* α-hemolysin, raising the prospect of new effective therapies against various pathogens that use pore-forming proteins (NICHD)
- Characterization of mammalian genes involved in iron-cluster synthesis and development of methods to assess cluster biogenesis, with implications for treatment of neurodegenerative and hematologic conditions such as Parkinson's disease and refractory anemias (NICHD)
- Discovery that cannabinoids mediate analgesia largely via peripheral CB1 receptors, which may help guide the development of peripherally restricted CB1 agonists as analgesics without any central side effects (NIAAA)
- Finding of excessive telomere loss and

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reduced T-cell immune function among caregivers of Alzheimer's patients, establishing a link between chronic stress, lymphocyte lifespan, and aging (NIA)

- Further elucidation of the DNA repair functions of FANCJ, the Fanconi anemia protein associated with FA complementation group J, based on studies demonstrating its interactions with proteins associated with breast and colon cancer; and the identification of replication protein A as the first regulatory partner of FANCJ in DNA repair and the maintenance of genomic stability (NIA)
- Finding, in a genome-wide search for genes with RNA polymerase II stalled within the promoter-proximal region, that regulated stalling of polymerase elongation occurs at hundreds of genes that respond to stimuli and developmental signals, establishing that polymerase stalling is an important mechanism in the regulation of gene transcriptional responses to dynamic environmental and developmental cues (NIEHS)
- Solving the crystal structure of DNA polymerase μ, providing new insights into the repair of potentially cytotoxic double-strand DNA breaks that can be induced by chemotherapeutic agents and by physical and chemical agents in the environment (NIEHS)
- Derivation of a detailed molecular model of the retromer cargo-recognition subcomplex by combining X-ray crystallography, computer-enhanced electron microscopy, and bioinformatic analysis, elucidating many of the cellular functions performed by the retromer complex, such as iron-transporter recycling and processing of the amyloid precursor protein (NIDDK, NIAMS, NICHD)
- Demonstration of a new function for RNA: playing a direct role in the repair of double-strand breaks in chromosomal DNA by serving as a template at the break site, potentially leading to new directions in gene targeting given that RNA can be amplified at will within cells (NIEHS)
- Discovery that the high-mobility group box 1 protein specifically interacts with the base excision–repair intermediate and accumulates at sites of oxidative DNA damage in living cells, suggesting that it serves as a novel base excision–repair cofactor (NIEHS)
- Identification of an enzymatic pathway that freezes the chromatin environment to ensure that DNA lesions are properly repaired (NIAMS, NCI)
- Demonstration that interleukin-2, acting via the transcription factor Stat5, promotes the differentiation of immunosuppressive regulatory T cells but inhibits the generation of proinflammatory T cells that produce IL-17 (NIAMS, NIAID, NIDDK)
- First demonstration that the "master" regulator MyoD requires an RNA helicase and a noncoding RNA to promote muscle gene expression and differentiation of skeletal muscle cells (NIAMS)
- Identification of the sphingolipid sphingosine-1-phosphate as an important regulator of allergic responses and the discovery of its possible role as a determinant of anaphylaxis (NIAMS, NIDDK)
- The finding of reduced occurrence of post-traumatic stress disorder among combat veterans who sustain damage to either of two brain areas—the ventromedial prefrontal cortex or an anterior temporal area that includes the amygdala—suggesting that these two areas are critically involved in PTSD (NINDS)
- The finding that GABAergic circuits are not engaged by thalamocortical input in the neonate, but are poised for a remarkably coordinated development of feedforward inhibition at the end of the first postnatal week, a critical event in the development of a functional circuit in the mammalian brain (NINDS)
- Demonstration that voltage-sensor paddle motifs are modular structural motifs in ion channels and in other voltage-sensitive membrane proteins and that they are important pharmacological targets (NINDS)
- Finding that new cell lines from mouse epiblast share defining features with human embryonic stem cells and can enhance understanding of how pluripotent cells generate distinct fates during early development (NINDS, NCI)
- Elucidation of biochemical mechanisms underlying the ability of the green tea polyphenol epigallocatechin gallate to stimulate production of nitric oxide from vascular endothelial cells and to inhibit hepatic gluconeogenesis, findings relevant to potential cardiovascular and metabolic health benefits of drinking green tea (NCCAM)
- Identification of a new endoplasmic reticulum chaperone protein, called the sigma-1 receptor, which under normal physiological conditions, senses and transmits the ER calcium level to mitochondria to increase bioenergetics and in deteriorating conditions translocates to the whole ER to promote cell survival by preventing protein aggregations—with implications for diseases in which sigma-1 receptors have a role, such as addiction, depression, amnesia, stroke, and cancer (NIDA)
- Finding that blockade of brain endocannabinoid CB1 receptors by AM251, a novel CB1 receptor antagonist, alters the breakpoint for intravenous cocaine self-administration and attenuates cocaine-enhanced electrical brain-stimulation reward, suggesting that AM251 or other more selective and potent CB1 receptor antagonists deserve further study as potentially effective anti-cocaine medications (NIDA)
- Demonstration by pharmacologic MRI that a novel dopamine D_3 receptor antagonist blocks the targeted receptors in the nucleus accumbens, the likely mechanism by which it produces anti-cocaine-like effects in vivo, suggesting that such compounds may be used to further elucidate the role of dopamine D_3 receptors in drug abuse and may serve as leads for therapeutic agents to treat addiction (NIDA)
- Demonstration on MRI that in youth with attention deficit hyperactivity disorder, the brain matures in a normal pattern but is delayed three years in some regions, on average, compared with that of youth without the disorder, suggesting that ADHD may be a disorder of brain-maturational delay (NIMH)
- Completion of the first prospective study of cortical brain development before and after the onset of pediatric bipolar disorder, revealing a distinct pattern of developmental change—asymmetric gains and losses of gray matter—compared with that of healthy youth and of those with childhood-onset schizophrenia (NIMH)
- The finding that a variation in a gene called *GRIK4*, which codes for a kainic acid–type glutamate receptor, appears to make people with depression more likely to respond to the medication citalopram than are people without the variation, suggesting that the glutamate system plays a role in modulating response to selective serotonin reuptake inhibitors (NIMH, NHGRI, NIAAA)
- Identification of a key step in the silencing of the *FMR1* gene that causes fragile-X mental retardation syndrome—SIRT1 deacetylation, a late event in gene silencing—suggesting that SIRT1 inhibition and reactivation of *FMR1* in neurons may be possible (NIDDK)

Development of new or improved instruments and technologies for use in research and medicine

- Development of novel techniques to map human histone methylations that showed correlations between chromosome banding patterns and unique histone modifications, as well as associations with chromosome breakpoints detected in TY cell cancers, providing new insights into the function of histone methylation and chromatin organization in genome function (NHLBI)
- Development of an ultrasensitive, faster method for detecting infectious prions using seeded conversion of recombinant prion protein, which should facilitate improvements in the practicality of diagnostic prion assays as well as in fundamental studies of structure and formation of the scrapie prion protein isoform (NIAID)
- Development of an automated lab-on-a-chip immunoassay for inflammatory biomarkers in newborns (NIBIB)
- Development of a microcalorimetric method to determine the thermodynamics of multiprotein complex assembly, with applications to signaling complexes important in T-cell activation (NIBIB, NCI)
- Use of a combination of solid-state nuclear magnetic resonance data and electron microscopy data to develop a full model of the molecular structure of amylin fibrils, a pancreatic peptide that may contribute to the destruction of insulin-producing cells in patients with type 2 diabetes, elucidating the generic propensity of peptides and proteins to form amyloid fibrils and potentially facilitating the development of therapeutic agents (NIDDK, NIBIB)
- Development of a novel procedure that allows rapid and accurate determination of a protein's three-dimensional structure using only chemical shifts as input data, applicable to proteins of up to 130 residues, but can be extended to larger sizes when supplemented with a small fraction of the commonly used regular NOE restraints (NIDDK)
- Development of a new equation to determine the cumulative energy deficit required to lose a pound of body weight that includes initial body fat in the calculation and accounts for why individuals with lower initial body fat require less than the 3,500-kcal deficit per pound of weight loss (NIDDK)
- Development of a third-generation human mitochondria-focused cDNA microarray (hMitChip3) and its bioinformatics tools: the chip consists of the 37 mitochondrial DNA-encoded genes, 1,098 nuclear DNA-encoded and mitochondria-related genes, and 225 controls, each in triplicate; the bioinformatic software includes data-analysis procedures and a customized database for interpretation of results (NCCAM)

Advances in imaging

- Development of a real-time system for intraoperative visualization of fluorescently labeled tissue, demonstrated on surgical resection in metastatic murine ovarian cancer (NIBIB, NCI, CIT)
- Demonstration that MRI can be used to guide X-ray procedures using conventional equipment to test cell therapies for heart disease (NHLBI)
- Development of an easily implemented imaging technique in the spatial frequency domain capable of acquiring both the scattering and the absorption distributions in a single exposure, which should help broaden the imaging applications of X-ray scattering (NHLBI)
- Development of a new fluorescence collection device—total emission detection—that greatly increases fluorescence light collection in a two-photon microscope, with the potential for decreasing photodamage and allowing for deeper imaging in thick tissue and faster imaging for dynamic studies (NHLBI)
- Development and demonstration of scanning transmission electron tomography for imaging cellular proteins labeled with heavy-atom cluster nanoparticles (NIBIB, NIDDK)
- The use of novel fluorescence imaging approaches combined with quantitative analysis and mathematical modeling to further elucidate cellular processes, such as membrane partitioning and its role in protein sorting and transport in the Golgi apparatus, biogenesis and turnover of peroxisomes, mitochondrial morphology and its regulation of cell-cycle progression, control of primary cilia dynamics, intercellular transfer between stem and niche cells, origin of autophagosomes, and PALM (live-cell photoactivation localization microscopy) for single-particle tracking (NICHD)
- Further elucidation of blood and lymphatic vessel formation during vertebrate embryogenesis through the development of confocal microangiography and high-resolution in vivo imaging of zebrafish blood vessels, elucidating a pathway of artery specification, establishing a role for neuronal guidance factors in vascular patternings, illuminating vascular tube formation in vivo, and identifying a lymphatic vascular system in zebrafish (NICHD)
- Improved MRI contrast and resolution that allows visualization of laminar cortical architecture of human brain based on magnetic properties of tissue (NINDS)
- Development of a method to combine measurements of intensities and photon trajectories with theory and simulations to rigorously determine distances in single-molecule FRET (fluorescence resonance energy transfer) experiments (NIDDK)
- Improvement on matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) with MALDI-ion mobility orthogonal time-of-flight MS (MALDI-IM-TOFMS) as a means to directly probe tissue to map and image distribution of analytes and elucidate molecular structure with minimal preparation (NIDA)

Advances in bioinformatics

- Introduction of dbGaP (database of genotypes and phenotypes) to archive and distribute genome-wide association studies and other data that explore the connection between phenotype and genotype, with the aim of facilitating research into the genetic causes of disease and accelerating the advance of personalized medicine (NCBI/NLM)
- Publication by the ENCODE Consortium of landmark papers that advance the collective knowledge of human genome organization, function, and evolution, including elaboration of transcriptional regulation and chromatin structure (NHGRI, NCI)

Development of new or improved approaches for preventing or delaying the onset or progression of disease and disability

- Identification of rapamycin as an effective agent for the prevention of tobacco carcinogen–induced lung tumors (NCI-CCR)
- Demonstration that complications of sickle cell disease, such as pulmonary hypertension, priapism, leg ulceration, and stroke, are directly linked to the intensity of hemolysis, providing new insights into treatments (CC, NHLBI)
- Development of a risk-assessment

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tool, called the CARE model, that provides a more accurate assessment of invasive breast cancer risk in African American women than the currently available NCI Breast Cancer Risk Assessment Tool (NCI-DCEG, NICHD)

- Identification of two new components of the Fanconi anemia (FA) core complex: FAAP 24 and FAAP 100, with implications for further understanding of the FA–breast cancer–associated DNA damage repair pathway and for screening potential anticancer drugs that facilitate or block interactions between the FA core complex and DNA (NIA)
- The finding that gynecomastia in three otherwise healthy prepubertal boys with normal serum concentrations of endogenous steroids was associated with the topical application of products that contained lavender and tea tree oils, both of which were found to have estrogenic and antiandrogenic activities in human cell-line studies (NIEHS)
- The finding that patients with rheumatoid arthritis who were treated with hydroxychloroquine were much less likely to develop diabetes mellitus than those not treated with hydroxychloroquine, suggesting this medication may be useful to prevent development of diabetes in those at risk (NIAMS)
- Completion of recruitment for the first phase I study of a whole-plant mistletoe extract given together with chemotherapy in patients with advanced solid tumors (NCCAM)
- Launch of an exploratory study to evaluate the ability of the green tea polyphenol epigallocatechin gallate to simultaneously improve metabolic and cardiovascular actions of insulin in healthy, obese, hypertensive, or diabetic subjects (NCCAM)
- Conduct of a clinical study of the role of endocrine-immune dysfunction in patients with active rheumatoid arthritis, aimed at gathering data that may provide further support for investigating selected CAM interventions, such as DHEA and stress-reduction techniques in similar populations of RA patients (NCCAM, NIAMS, NCI, CC)

Vaccine development

- Identification and structural definition of a site of vulnerability on the HIV-1 Env gp120 glycoprotein that is recognized by the broadly neutralizing antibody b12 and is involved in the attachment of gp120 to CD4 (VRC/NIAID, NCI)
- Identification of mutations in influenza A subtype H5N1 (avian) hemagglutinin (HA) that alter its specificity for sialic acid (SA) either by decreasing α–2,3-SA or increasing α–2,6-SA recognition, a finding that can guide the development of preemptive vaccines and therapeutic monoclonal antibodies that can be evaluated before the emergence of human-adapted H5N1 strains (VRC/NIAID)
- Identification in patient sera of a potent and broad HIV-1 neutralization capacity mapped to the primary receptor CD4 binding region of HIV-1 Env gp120 glycoprotein, a finding that could lead to improved vaccine immunogens (VRC/NIAID)
- Finding that preserved central memory CD4+ T lymphocytes are associated with prolonged survival in pathogenic SIV-challenged monkeys immunized with plasmid DNA and replication-defective adenoviral vectors encoding SIV proteins, with implications for immune correlates of vaccine efficacy in humans (VRC/NIAID)
- Finding in a mouse model that the highly lethal 1918 pandemic influenza virus is susceptible to immune protection by a preventive hemagglutinin DNA vaccine (VRC/NIAID)
- Identification of new antigens that may be potential targets for new therapeutics or vaccines to help control malaria (NIAID)
- Development of a vectored vaccine delivered nasally that protected rhesus monkeys against Ebola virus challenge, in the first study in which topical immunization through the respiratory tract achieved prevention of a viral hemorrhagic fever infection in a primate model (NIAID)
- Demonstration of the immunogenicity and induction of protective immunity by recombinant hepatitis C virus–like particles (HCV-LP) in chimpanzees; immunized animals developed HCV-specific cellular immune responses (NIDDK)

Development of new or improved ways to diagnose disease and disability

Gene expression patterns

- Expression profiling to develop new biomarkers for liver cancer and to reveal a signature of high cancer risk in benign tumor (NCI-CCR)
- Characterization of the clinical manifestations of children with Hutchinson-Gilford progeria syndrome, including sclerotic skin changes, joint contractures, bone abnormalities, alopecia, growth impairment, elevated blood pressure, reduced vascular compliance, low-frequency conductive hearing loss, functional oral deficits, abnormal prothrombin times, and elevated platelet counts, setting the stage for the evaluation of interventional therapies (NHGRI, CC, NHLBI, NIDCD, NIDCR, NICHD, NEI, NCI, OD)
- The finding that gene-expression patterns derived from blood cells are a near-match to liver gene-expression patterns and predict acute acetaminophen exposure in rats more reliably than traditional clinical parameters, suggesting a means to ascertain exposure levels well before liver damage is detected by classical parameters and supporting the potential use of genomic markers in the blood as surrogates for clinical markers of potential acute liver damage (NIEHS)

Development of new or improved ways to treat disease and disability

- Blood levels of NF-κB–related serum factors found to be biomarkers of therapeutic response and survival in patients treated for advanced oropharyngeal cancer (NIDCD, NCI)
- Development of darunavir (approved by the FDA) and other protease inhibitors that block the dimerization process of HIV-1 protease (NCI-CCR)
- New data from adult nephropathic cystinosis patients seen at the NIH Clinical Center from 1986 to 2006 showing that chronic oral cysteamine therapy results in taller and heavier individuals with lower cholesterol levels and lower frequencies of myopathy, diabetes, pulmonary dysfunction, hypothyroidism, and death, pointing to cysteamine as the treatment of choice for cystinosis patients of all ages (NHGRI)
- Improvement in the rate of gene transfer in patients with adenosine deaminase deficiency by using chemotherapy to reduce the number of patient marrow cells to make room for the corrected ones, with subsequent marked improvement in T-cell numbers and immune function (NHGRI, NCI, NHLBI, NIDDK)
- High-dose idebenone shown to improve neurological outcome in patients with Friedreich's ataxia in a randomized controlled trial (NINDS) ■

Coming Clean on Cell Line Contamination

continued from page 1

might be cross-contaminated or improperly characterized, according to peer-reviewed papers published in recent years. The issue has been addressed in the pages of *Science*, *Nature*, and other prominent journals and has prompted position statements from professional organizations. Yet the problem lumbers on largely unabated.

Cell-line cross-contamination commonly refers to when a foreign cell, usually mammalian, is introduced inadvertently into a culture of living cells and becomes a resident of that culture, either coexisting or entirely replacing the original line. Contamination from bacteria, yeast, and other invaders is also problematic, but for the most part researchers know how to identify or prevent this kind of contamination.

"We are fundamentally in agreement that misidentified and contaminated cultures constitute a serious, ongoing problem," said Michael Gottesman, deputy director for intramural research. "What is debated is how to best eliminate it."

The NIH intramural and extramural programs have stopped short of mandating cell-line authentication as a requirement for funding. The reasoning is that authentication methods can be specific and are continuously evolving, making it impractical for NIH to require application of particular methods, as relayed in an NIH policy notice issued on November 27, 2007, posted at

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-017.html>.

For now, in lieu of a consensus statement, Gottesman and Norka Ruiz Bravo, deputy director for extramural research, advocate awareness and diligence. They would like to see the cell-line cross-contamination and misidenti-fication addressed in the peer-review process, while educating scientists on their responsibilities to characterize their model systems.

The NIH policy notice, entitled "Notice Regarding Authentication of Cultured Cell Lines," was in response to an open letter sent to DHHS Secretary Michael Leavitt, dated July 7, 2007, by Roland Nardone, professor emeritus at The Catholic University of America in Washington, D.C., and co-signed by 18 other cell biology experts from the United States and United Kingdom.

This letter, posted at

<http://cellbank.nibio.go.jp/cellbank/qualitycontrol/OL7-11-07.pdf>,

calls for a "no authentication/no grant" approach by NIH, as well as for journals to require proof of authentication as a requirement for peer-review publication.

"The NIH notice strongly suggests that peer reviewers of grants and manuscripts could be the key to compliance," said Nardone. "I do not subscribe to that view because the pool of reviewers lacks the background knowledge and it will be some time—if ever—before that hole in the fence gets closed."

He noted that the FDA has a requirement for cell-line authentication as a condition for drug approval. NIH, he said, has a different culture and feels such an approach would be dogmatic.

NIH Director Elias Zerhouni has since tasked Nardone with bringing together a diverse group of scientists, scientific societies, grant reviewers, and scientific publishers to establish a consensus policy.

Nardone leads a campaign started in the 1960s by Walter Nelson-Rees, a biologist then at the University of California, Berkeley, who discovered that more than 40 individual cell lines had been overtaken by HeLa cells, cervical cancer cells cultured from a Baltimore woman's tumor in the early 1950s.

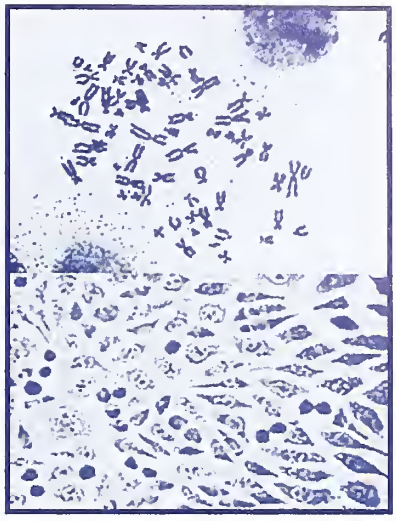
Nelson-Rees alienated some scientists with his series of papers in the early 1970s in *Science*, naming labs and false cell lines and calling on the community to re-evaluate research based on these cell lines.

"The problem was reported to be widespread, so much so that it encouraged disbelief," Nardone said. Yet the problem has not gone away and may have gotten worse, he observed

"Cell lines shown in 1966 to be misidentified or cross-contaminated are still being used as if they were the real thing," Nardone said, referring to a publications database search he conducted with colleagues.

To minimize the risk of contamination or misidentification, Nardone offers four points of action, which the NIH Office of Intramural Research also endorses:

- Primary cultures and finite cell lines (for example, noncancer) should be sufficiently characterized to confirm their source, such as species, tissue type, or the individual for human cells, if relevant; even primary cultures can become cross-contaminated.
- Continuous cell lines should be shown to be authentic using genetic profiling or an equivalent test of similar stringency.



from the Cell Line Authentication Global Awareness Initiative website: <http://cellid.cua.edu>

- Obtaining cell lines from the originator should not be construed as sufficient evidence of their identity.
- Whenever possible, cell lines should be obtained from a major repository that has a rigorous program of cell-line authentication. Doing so does not absolve the investigator, however, of the responsibility to confirm independently and monitor authenticity as experimental use of the cells continues.

Nardone lists various techniques for authentication, such as karyotyping, isoenzyme profiling (developed by Stephen O'Brien of NCI), and DNA fingerprinting, in his white paper entitled "Eradication of Cross-Contaminated Cell Lines: A Call for Action," now published in *Cell Biology and Toxicology* and posted at

<http://ori.dhhs.gov/education/CellContamination.shtml>.

DNA profiling, although usually not possible in most small labs, is becoming increasingly affordable to outsource, according to papers by Charles Patrick Reynolds of the University of Southern California in Los Angeles and by John Masters of University College London.

Nardone and his colleagues recommend short-tandem repeats as an effective method of profiling. They also recommend improved laboratory practices, such as working with only one cell line or cell lineage in the hood at one time and never sharing reagents, what he called the cardinal rule. ■

Backgrounders

The NIH intramural community can learn more about cell-line contamination and safe laboratory practices in two courses offered by Bio-Trac*, the Biotechnology Training Courses. These are "TRAC 36: Cell Line Identification & Authentication" and "TRAC 7: Animal and Human Cell Culture: Method and Applications."

Online information can be found at Cell Line Authentication Global Awareness Initiative:

<http://cellid.cua.edu>.

An unofficial list of contaminated cell linescan be found at:

<http://en.wikipedia.org/wiki/List_of_contaminated_cell_lines>

***Ed. note:** Bio-Trac is offered through FAES under a contract with R/M Nardone Associates, Inc., a successor to a company founded by Roland Nardone.

From OITE

Career Symposium on Tap

The First Annual NIH Career Symposium will be held Wednesday, **April 9, 2008**, from 7:30 a.m. to 5:00 p.m. in the Natcher Conference Center.

Organized by the Office of Intramural Training and Education (OITE), in collaboration with the Graduate Student Council, NIH Fellows Committee, and the Foundation for Advanced Education in the Sciences, the symposium aims to provide NIH trainees with solid information about career options across science and medicine and the opportunity to network with established professionals in these fields.

There will be 15 panel sessions—on scientific writing, education, grants administration, public policy, clinical job options, research-intensive careers, and careers away from the bench. Panel speakers include government science policy advisors, patent and grant directors, scientific consultants, medical directors of pharmaceutical companies, and university professors.

Skills workshops will address networking, leadership, and work-life balance. There will be ample time during lunch and at a reception after the event to interact with speakers (and practice networking skills).

The career symposium also marks the official opening of the Career Services Center in the OITE. The center has been in operation for several months (see *The NIH Catalyst*, Jan.-Feb. 2008) and is staffed by professional career counselors. It provides guidance on career directions, options, and self-evaluation, as well as assistance with interviewing, networking, and CV and résumé development.

All trainees and mentors are encouraged to attend the symposium. For more information or to register, visit the OITE website:

<http://www.training.nih.gov>.

—Caroline Small

Graduate Student Council Update

NIH currently has 532 graduate students who hail from an array of academic programs and universities around the country.

The Graduate Student Council (GSC) was formed to create a community for these students and to ensure that NIH has the resources this population needs.

Since the GSC was established in 2001, active membership has ranged from 5 to 8 percent of the graduate student population. The council has had the help of the Graduate Partnership Program (GPP) in organizing retreats, symposiums, and career development activities; and more recently the NIH Fellows Committee (FelCom) and the Foundation for the Advancement of Education in the Sciences (FAES) have added their support.

Graduate students have been gaining experience teaching an FAES survey course on various laboratory techniques and are currently working closely with FelCom, FAES, and the GPP to expand teaching opportunities for both graduate students and postdocs. The GSC also offers new graduate students the option of pairing up with a student peer mentor.

Among newer developments are student-run scientific interest groups, a community service group, *The GSC Chronicles* student newsletter, a seminar series, and a recently crafted constitution that delineates the official duties of the GSC representatives and various committee chairs.

At a recent retreat, the GSC decided to create a student-financed budget and to focus on increasing graduate student community participation in GSC decision making, strengthening the relationship of the graduate student population to NIH as a whole, and resolving graduate program–specific conflicts.

To find out more about the GSC and upcoming graduate student–sponsored events and to read GSC meeting minutes and *The GSChronicles*, visit the GSC website:

<http://gpp.nih.gov/Current/GraduateStudentCouncil/>.

—Vanessa McMains

From FelCom

Announcing FARE 2009

The NIH Fellows Committee (FelCom) is sponsoring the 15th annual Fellows Award for Research Excellence (FARE 2009) competition.

Winners receive a $1,000 travel award to be used between Oct. 1, 2008, and Sept. 30, 2009, to present their research at a scientific meeting. Every year, about 25 percent of FARE applicants receive this award.

Any fellow with fewer than five years postdoctoral experience is encouraged to submit an abstract. Pre-IRTAs doing doctoral dissertation work and visiting fellows not already tenured at a foreign institution are also eligible.

Mentors are encouraged to notify their fellows of this opportunity, which has a relatively painless application process and higher odds of success than most fellows' awards.

Applications must be submitted electronically (**March 14–April 14, 2008**) at the "subcommittees/FARE" link of the new FelCom website:

<http://felcom.od.nih.gov/

Applications will be judged on scientific merit, experimental design, and overall quality and presentation. Winners will be announced by September 1 and are expected to present their work at the FARE 2009 awards ceremony and to serve as judges for the 2010 FARE competition.

Fellows, staff scientists, and principal investigators are encouraged to volunteer to serve as study section judges for one of the 50 study sections. For more information, contact one of your institute's FelCom representatives:

<http://felcom.od.nih.gov/members.aspx>.

—Bobbie Ann Austin

On Tenure Track

Christopher Wanjek

Rajat Varma

Rajat Varma, head of the new T-Cell Biophysics Unit in NIAID's Laboratory of Cellular and Molecular Immunology, came to NIH in December from New York University to study immune cell signaling.

Varma hopes to uncover the relationship between transcription factor activity and T-cell receptor triggering events at the surface in living cells. He also will investigate how information is relayed along antigen and cytokine receptors by digging down to nanometer scales with optical techniques such as fluorescence resonance energy transfer (FRET) microscopy and fluorescence correlation spectroscopy.

The first part of this project entails developing optical tools. Varma is now assembling his lab in Building 4, equipping it with state-of-the-art imaging systems. He is interested in developing tools to study transcriptional activity in living cells by using fluorescence anisotropy imaging to estimate the proportion of GFP-tagged transcription factors bound to DNA in the nucleus. He hypothesizes that a balance of transcription factor activity downstream of T-cell receptors governs T-cell differentiation and tolerance.

Varma's research has followed a path from physics to cell biology and, like the optical techniques he draws upon, has tunneled him deeper into immunology. As a doctoral candidate in India, he and his colleagues discovered how glycosylphosphatidylinositol-anchored proteins are organized in submicron domains at the cell surface, and the methodology he used with FRET microscopy offered a new way to monitor nanometer-scale associations between molecules in living cells.

As a postdoc at NYU's Skirball Institute for Biomolecular Medicine, Varma found that T-cell receptor–proximal signals are sustained in peripheral microclusters and terminated in the central supramolecular activation cluster. At NIAID he will probe cell nuclei using influenza as a model system.

—Christopher Wanjek

Recently Tenured

Sanjay A. Desai *received M.D. and Ph.D. degrees from Washington University Medical School in St. Louis in 1992. After an internal medicine residency and infectious diseases fellowship at Duke University Medical Center, in Durham, N.C., he joined the Laboratory of Malaria and Vector Research, NIAID, in 1998. He is currently a senior investigator and chief of the Molecular Physiology Section, LMVR, NIAID.*

My laboratory has focused on the cell biology and physiology of the malaria parasite, *Plasmodium falciparum*. We are particularly interested in how malaria parasites acquire nutrients and other essential solutes from the human bloodstream.

Sanjay Desai

While growth inside host erythrocytes facilitates evasion of immune responses, it complicates acquisition of nutrients from serum. Many essential nutrients are not present in red cell cytosol and have inadequate host cell permeability to sustain parasite demand. This problem had been recognized for decades, but the molecular mechanisms used to overcome it were unknown. My laboratory identified two unusual ion channels that appear to resolve this dilemma.

One channel, the plasmodial surface anion channel (PSAC), is present on the infected erythrocyte membrane but absent from uninfected cells. Its unique functional properties along with two mutants we generated through in vitro selection strongly suggest PSAC is encoded by the parasite and trafficked out to the host membrane.

Striking among PSAC's functional properties is that it permits negligible Na^+ uptake despite broad permeability to needed sugars, amino acids, purines, organic cations, and some vitamins.

This selectivity profile is unprecedented among other ion channels; it is also important for parasite survival because Na^+ exclusion is required to maintain infected erythrocyte osmotic stability in plasma.

We determined that a major contributor to PSAC's solute selectivity is electrostatic repulsion of Na^+ by cationic residues situated at the extracellular pore mouth. The significant permeability of organic cations indicates that additional features, presumably acting via an as-yet-unidentified selectivity filter in the pore, must also contribute to Na^+ exclusion.

PSAC's strict conservation in all plasmodia suggests it may be a target for antimalarial development. To test this hypothesis, we found high-affinity PSAC antagonists through high-throughput screening with a quantitative transmittance-based assay developed by my group. These antagonists sterilize in vitro parasite cultures.

There is also a good correlation between these antagonists' affinity for PSAC and their parasite growth inhibitory concentrations, fulfilling a classical test of target validation in drug development. The Medicines for Malaria Venture, a Geneva-based public-private partnership that seeks to discover and develop new antimalarial drugs, has recognized PSAC as an important target and has accepted our project into their portfolio.

The second ion channel we identified is a large conductance channel on a specialized membrane, the parasitophorous vacuolar membrane, surrounding the intraerythrocytic parasite. This channel appears to provide the parasite with direct access to metabolic precursors in RBC cytosol and may also be a good drug target.

Eric Engels

Major ongoing areas of investigation in the laboratory include 1) identification of the genes responsible for these and other parasite transport mechanisms with molecular, genetic, and biochemical approaches, 2) functional characterization of these transport proteins with the goal of understanding their structures and physiological roles, and 3) antimalarial drug discovery and development using novel, high-affinity PSAC antagonists.

Eric Engels *received his M.D. degree from Harvard Medical School in Boston in 1991. He trained in internal medicine at Brigham and Women's Hospital, Boston, and in infectious diseases at Tufts University School of Medicine, Boston, before joining NCI in 1998 as a senior staff fellow in the Viral Epidemiology Branch. He is currently a senior investigator in that branch, recently renamed the Infections and Immunoepidemiology Branch, NCI.*

As an epidemiologist in NCI's Division of Cancer Epidemiology and Genetics, my research focuses on the role of infection, immunity, and inflammation in the etiology of cancer. This work is grounded in my long-standing clinical interest in HIV and other infectious diseases and in a keen appreciation for quantitative approaches to epidemiologic questions.

A major component of my research aims at improving our understanding of cancer among people with HIV/AIDS. This research uses data from my HIV/AIDS Cancer Match (HACM) Study, which links HIV/AIDS and cancer registry data from 13 U.S. regions to identify cancers arising in more than 630,000 HIV-infected people.

The HACM Study allows me to examine patterns of cancer incidence that have direct public health relevance. I recently used this resource to describe trends in cancer risk among people with AIDS over the course of the AIDS epidemic from 1980 to 2002. I documented substantial declines in Kaposi sarcoma and non-Hodgkin lymphoma (NHL) over time, and a steep unexpected rise in Hodgkin lymphoma risk.

My interest in cancers in transplant recipients, another immunosuppressed population, evolved from my work on HIV/AIDS. I lead a major collaboration with the Health Resources and Services Administration, which oversees the U.S. transplant network. Together we are conducting a computerized match of U.S. transplant and cancer registries.

Our Transplant Cancer Match Study will obtain population-based cancer data on approximately half of the U.S. transplant population. The coupling of data in the transplant registry regarding demographics, cancer-related exposures (for example, viral infections), and medications, with detailed information from the cancer registries, will create a unique research resource.

Having observed a remarkably high risk for lung cancer among HIV-infected people in the United States, I questioned the common assumption that frequent tobacco use entirely explains the elevation. I have now conducted several retrospective cohort studies of lung cancer among HIV-infected persons.

Recently Tenured

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Using various statistical methods to adjust for the effects of tobacco, each study has demonstrated that lung cancer risk is higher in HIV-infected people than predicted from the effects of smoking alone. We are now developing epidemiologic approaches to test the hypothesis that other processes, such as inflammation, play a role in promoting lung damage among HIV-infected individuals. In several other studies, I am currently evaluating chronic *Chlamydia pneumoniae* infection, pulmonary scarring, and pneumonia and tuberculosis as risk factors for lung cancer.

My interest in NHL also stems from the high risk seen in people with HIV/AIDS, as well as my belief that other infections and immune-related conditions are important. Building on my prior work on the epidemiology of human herpesvirus 8 (HHV8), I described the first case of an HHV8-positive NHL in Africa. I also conducted a large retrospective cohort study of hepatitis C virus (HCV) and risk of lymphoproliferative malignancies in U.S. military veterans. This study showed an association with NHL and, for the first time, an increased risk for the related malignancy Waldenström macroglobulinemia.

Finally, my official duties include work as a physician in the Johns Hopkins Hospital HIV clinic in Baltimore, where I attend for one full day every two weeks. Most of my patients there have complex medical problems, such as HCV-related liver disease and tobacco-induced lung disease, compounded by such social problems as substance abuse, poverty, and homelessness.

It has been rewarding to follow these patients over an extended period of time and to see the beneficial effects of HIV therapy advances. This work provides the opportunity to use my clinical skills to help an underserved population, and it motivates and grounds my research activities.

Charles Rotimi *received his Ph.D. degree in epidemiology from the University of Alabama, Birmingham, in 1991. He did his postdoctoral work at Loma Linda (Calif.) University and Loyola University Chicago–Stritch School of Medicine in Maywood, Ill., and in 2004 became the director of the National Human Genome Center at Howard University College of Medicine in Washington. He joined NHGRI in late November 2007 as the first director of the new NIH Intramural Center for Genomics and Health Disparities.*

Research activities in my laboratory are directed at understanding the patterns and determinants of common diseases in populations of the African Diaspora, with particular focus on the triangular relationship between obesity, hypertension, and type 2 diabetes (T2D).

Fran Pollner

Charles Rotimi

Recent African-origin populations provide unique opportunities to study how "old" genes interact with "new" environments in the evolution of common complex diseases. Taking advantage of the huge contrast in the distribution of risk factors at the genetic and environmental levels in contemporary African populations, my lab uses genetic epidemiology and population genetics models to study the determinants of obesity, hypertension, diabetes, and associated complications.

We are particularly interested in generating data to explain phenomena such as the "thrifty genotype" hypothesis, which postulates that some genes in humans have evolved to maximize metabolic efficiency—as reflected, for instance, in lipid storage and food-searching behavior—and that in times of abundance, these genes predispose their carriers to diseases caused by excess nutritional intake, such as obesity and T2D.

My lab is leading an international team of investigators to understand how inherited factors in combination with lifestyle increase the risk of or resistance to T2D. The name of this novel project is "Africa America Diabetes Mellitus (AADM, pronounced Adam) Study." It was originally designed to identify diabetes genes in West Africa, the geographical origin of most African Americans. It has expanded to include sites in East Africa and China.

The AADM project has enrolled more than 4,800 persons with diabetes and control subjects, and it is contributing significant data to the global effort to understand the genetic basis of T2D.

In collaboration with colleagues in Iceland (deCODE Genetics), we recently identified three genes that are likely to play a major role in the risk of getting diabetes.

The first gene, called *TCF7L2*, is arguably the most important gene identified for diabetes to date and was identified using the genome-wide association strategy involving thousands of persons with diabetes and control subjects.

The second gene, called *CDKAL1*, influences insulin response. Persons who have two copies of this gene have a blunted insulin response compared with those who carry only one copy or are noncarriers.

The third gene, *TCF2* (*HNF1b*), associated with increased prostate cancer risk, may confer protection against T2D—an important finding that may help us understand the inverse relationship previously observed between the risk of diabetes and prostate cancer and that may have prevention and treatment implications.

Research resources available through the AADM project have facilitated multiple international collaborations, including: 1) an ongoing project in Joan Marini's lab at NICHD on the genetic basis of osteogenesis imperfecta caused by mutation in the *LEPRE1* gene; 2) a genome-wide association study of hypertension in African populations in Richard Cooper's lab at Loyola University in Chicago; 3) a study of the genetics of Bardet-Biedl syndrome in African patients—the role of novel mutations in the *BBS5* gene; and 4) the population genetics of the hypervariable region of the mtDNA.

In collaboration with investigators at the Coriell Institute for Medical Research in Camden, N.J., my lab is using the Affymetrix Genome-Wide Human SNP

Patent Law/Tech Transfer IG

A new interest group focused on patent law and technology transfer is hoping to attract individuals currently at the NIH Office of Technology Transfer, bench scientists with interests in intellectual property, and former fellows who have transitioned into related careers in local companies. The group will hold seminars with invitees from the U.S. Patent and Trademark Office, law firms, and biotechnology and pharmaceutical companies. Contact Cameron Good **<goodc@mail.nih.gov>** or Thomas Paul **<paulth@mail.nih.gov>**.

Array 6.0 with 1.8 million genetic markers to perform the first genome-wide association scan of an African American cohort to search for genes associated with obesity, hypertension, diabetes, and the metabolic syndrome.

The more than 2,000 related and unrelated African Americans included in this study were enrolled and examined by my lab.

In collaboration with Julie Palmer of Boston University, my lab is participating in the Black Women Heart Study—a national longitudinal cohort of women assembled in 1995 to study causes of illness in black women. It includes 59,000 women aged 21–69 at baseline. My lab has been responsible for receiving, isolating, and tracking DNA samples from more than 25,000 women. This is a national resource that is making significant contribution to our understanding of major health outcomes (for example, diabetes and lupus) in women, with special focus on African American women.

I am the founding and current president of the African Society of Human Genetics (AfSHG), which was formed to engage African researchers, and other researchers interested in Africa, in genomic research.

Since its inception the society has provided a forum for African scientists and students to interact and exchange information in the field of genomic research. In collaboration with scientists from Ethiopia, the United Kingdom, and the United States, my lab is involved in a Wellcome Trust–funded project to understand the genetic basis of podoconiosis.

Lower legs of patient with podoconiosis in his 20s, showing asymmetric nodular disease

A model for gene-environment interactions, podoconiosis (endemic nonfilarial elephantiasis) is a geochemical disease occurring in individuals exposed to red clay soil derived from alkalic volcanic rock. One of the striking features of podoconiosis is that only a small proportion of individuals who are exposed to red clay develop disease. Investigators involved in this project met under the umbrella of the AfSHG, and I anticipate that AfSHG will provide a wonderful forum for my lab and attract minority and African students and investigators to multiple labs at NIH.

Finally, I believe that scientific activities operate within the larger context of societies and that the junction of society and science constantly has to be managed so as not to trample on the independence required for good scholarly investigation or to alienate members of societies from the scientific process.

In this regard, my lab is interested in how scientists document and describe the nonrandom pattern of human genetic variation and its link to disease risks in different populations. For example, how does human genetic variation inform our understanding of self and group identity and differential distribution of diseases? We are directly involved in these debates and hope to inform the interpretation of human genetic variation within the context of health disparities and group identity. ■

Visiting Fellows Expo

The fifth international exposition for NIH visiting fellows will be held Thursday, **May 15, 2008**, at the Natcher Auditorium.

The expo is organized by the NIH Visiting Fellows Committee, which has sent invitations to 38 embassies and 12 companies and welcomes the attendance of the 2,821 visiting fellows currently on campus.

Steven Buchsbaum, senior technology strategy officer for global health discoveries, of the Bill & Melinda Gates Foundation, will speak from 11 a.m. to noon, after which the expo will follow from noon to 4:00 p.m.

For more info, visit the Visiting Fellows Committee website: **<http://felcom.od.nih.gov/subCommittee/vfc/index.aspx>**.

Foreign Scientists at NIH by Country*

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Slovak Republic, 14
Slovenia, 2
South Africa, 7
Spain, 45
Sri Lanka, 5
Sweden, 27
Switzerland, 11
Syria, 1
Taiwan, 43
Thailand, 17
Tunisia, 4
Turkey, 18
Ukraine, 12
United Kingdom, 91
Uruguay, 2
Venezuela, 3
Vietnam, 2
West Bank, 1
Total active = 2,821

* **as of September 24, 2007**

Source: Division of International Services, NIH

Catalytic Reactions?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2E26.**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

In Future Issues...

- Framingham's New Home
- Copyright Issues
- Sequencing The Microbiome

Kids' Catalyst: Psst . . . Want to hear something?

Hey! Hey!! Please put those headphones down for just a minute and listen. Thank you. What? You can't hear me so well because the music was loud and your ears are ringing? Just give it a few minutes—and read a little bit about the ear in the meantime.

Our ears are complex, sensitive, and capable (in theory, if not in practice) of detecting sound signals that are very low or very high in both tone and intensity.

The terms "tone," "frequency," and even "pitch" are sometimes used interchangeably. Someone like your little sister most likely has a high voice—a high-frequency voice. Your dad's is usually much, much lower. If you ask someone to play 440 hertz (or Hz, the unit frequencies are measured in), they'll stroll over to a piano and hit the A above middle C—the audio frequency reference. Your sister's voice is much higher than that.

"Intensity" is how loud something is, measured in decibels. The intensity of parents quietly plotting where to hide your present is about 20 decibels (or dB, the unit used to measure loudness). That music you were just listening to is 80–100 dB—or more. No wonder your ears hurt.

As a side note, how much louder is 80 dB than 20 dB? You get to look that one up yourself, but a hint for you is that it's probably not what you think. Then you can also look up dB "sound intensity levels" versus "dB sound power levels"—and teach me about it!

The normal tone range of the human ear is 20–20,000 Hz. Actually, we're exposed to more than 20,000 Hz all of the time, we just don't hear it (so that's okay). Not so with decibels: If you're listening to something louder than 85 dB for a long time, it can cause gradual hearing loss, and more than 110 dB for more than a minute may bring permanent hearing loss.

So if you want to keep on enjoying the ability to hear soft conversations about where gifts for you are hidden, you might want to turn the music down. It's good for your snooping future. I know it's not so easy. After all, headphones are great because you hear what no one else hears and no one is asking you to turn the noise down in the middle of the night.. But though others may not be bothered by your loud music, you will be when you just can't quite make out what people are whispering about.

For more information about the ear, how to protect it, and much more, go to **<www.nidcd.nih.gov/health/hearing/>**.

—Jennifer White

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